

# Why Should **FDA** Regulate Drugs?



An Interview with **Janet Woodcock, M.D.**  
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## **What Is CDER's Mission?**

CDER's mission is to promote and protect the public health by ensuring that safe and effective drugs are available to Americans. This is a very succinct mission statement, but it encompasses a lot of activities.

## What Are the Public's Expectations of Drug Regulation?

The public's expectations—and the drug regulatory system that meets them—have been evolving over the course of the 20th century. Since the early part of this century, the public's basic expectations have been that all marketed drugs should be effective and safe within the context of their use and that unsafe or ineffective drugs should be kept off the market.

Another long-standing expectation of people is that human drugs should be of high quality, because poor quality drugs threatened the lives of many Americans early in this century. Also, there had been cases of false and fraudulent claims made for drugs, as well as false and misleading advertising. Americans expect the system to take care of that.

A more recent imperative is that the drug regulatory system must allow generic competition to help maintain reasonable prices for drugs and to help control healthcare costs. Clearly, it is an expectation of various groups that the generic industry should flourish and that it should set a standard for drug pricing in the United States.

Over the past decade, it has become very important to many Americans that seriously ill patients who lack treatment alternatives should have access to investigational drugs. Another expectation that is becoming more and more widespread is that all patient groups should have information for their patients about how to use approved drugs. For example, there should be information available on how to use drugs for children. Use of approved drugs should be studied enough in children so that pediatric information and, perhaps, formulas are available. Also, there are growing expectations that information about drugs—targeted at specific vulnerable populations such as the elderly and

women—will be made available, and that the drug regulatory system will somehow make this happen.

Finally, Americans realize that while it is important to keep unsafe and ineffective drugs off the market, a robust and flourishing drug development research program is also necessary in this country. Americans expect the drug regulatory system

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will get drugs through the pipeline, make them available to patients rapidly, and ensure all studies on human subjects are ethical and safe.

## What Has CDER Done to Improve Service to the Public?

For a long time, people lauded the quality of the CDER drug review process, but criticized it for being too slow. FDA began to address the issue in 1993 with the establishment of user fees. Since the industry is receiving a service from the government through CDER's review of its marketing applications, many felt industry should contribute directly toward the costs of the review process. Congress, industry, and FDA negotiated the user fee program. Industry pays fees to add to FDA's resources for reviewing new drug applications. In exchange, FDA makes a commitment to meet certain goals for review times.

CDER has been meeting all those goals. In fact, it has exceeded almost all of the goals, and it expects to

continue to exceed them. Basically, the number of new approved drugs has doubled, and the review times have been cut in half. The program has been so successful that it has been renewed for five more years, as part of the FDA Modernization Act of 1997. The approval process has been further improved by CDER's accelerated approval procedure.

Under this procedure, drugs for serious and life-threatening diseases can be approved before CDER is positive the drugs will help someone. CDER does this on the condition that there are indicators—called surrogate endpoints—that can allow us to reasonably predict that the drug will provide some benefit. The manufacturer still must continue clinical testing after the drug is made available, but patients with life-threatening diseases benefit by getting the drugs they need faster.

For instance, under this program, CDER approved the protease inhibitors used to treat HIV infection. Many Americans who have started therapy with these drugs have had their health restored to them and have returned to productive lives. All of the protease inhibitors were approved in a matter of months; one was approved in only 42 days. A major decline in AIDS-related deaths in the United States is partly attributed to the availability of these drugs.

### What Assurance Does the Public Have That FDA Regulation Will Be Balanced?

I believe quite strongly that a democratic government has to be fair. It's one of the principles of our society. One of the reasons that the citizens are willing to give power to the government is that the government is perceived as being fair and just. This requires balanced regulation, and that is why I have emphasized consistency in regulatory matters and policy, professionalism, and evenhandedness.

I also feel that human beings work together better in a nonadversarial manner. An adversarial relationship, although sometimes necessary, is not the best way to conduct public affairs. It wastes a lot of resources, and it doesn't get the best results. A by-product of working closely with industry, consumer groups, Congress, and the public is that you are much more likely to get balanced regulation.

In the regulatory area, we are talking about the exercise of federal power over other citizens in this country. It requires professionalism, tact, diplomacy, and a whole set of skills that may not be required in other areas.

### Why Not Trust Consumers to Decide for Themselves Which Medicines Work for Them?

I don't think it's in the government's best interest to stand between people—especially those who are desperately ill—and their desire to take particular medicines. But this libertarian issue shouldn't be confused with the scientific issue of whether patients can tell what medicines work, because with almost any drug treatment we use today, they can't tell.

Doctors thought for years they could tell what worked. In the 1960s, for example, doctors were

convinced that diethylstilbestrol, or DES, was terrific for preventing early miscarriages, and they gave it to thousands of women in pregnancy. "The women had miscarriages before, and I put them on this DES, and some of them didn't have miscarriages. So obviously, it's very effective," doctors thought.

In fact, when DES was actually subjected to scientific testing, it had no effect on miscarriage whatsoever. Not only was it absolutely ineffective, but unfortunately, it had delayed negative health effects on the fetus.

FDA who said the drug ought to be tested. NIH set up a trial, and what they discovered shocked everyone: Yes, the drugs make the beats go away, but the people who were put on the drugs had sudden death at a substantially higher rate than the people who were just left having the beats. The drugs actually made the problem worse, and maybe more likely to occur.

Even the people who did the trial were later haunted by the fact that they had given some people that drug. They were people whom the researchers knew, and some of them died.

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We had a more recent experience like this with a heart rhythm drug. After people have heart attacks, they can have extra beats. And it's known that a percentage of people with those extra beats will have sudden death. Well, drugs were discovered that made the sudden beats go away, and people thought, "Wonderful! Make the beats go away, and sudden death will go away." The medicine became the standard of practice throughout the United States; everybody was using the drug.

There were some skeptics at the National Institutes of Health and

So the answer is, many, many very smart people have thought they knew what drugs would help them and what drugs would hurt them, and clinical tests again and again have proven them wrong. They didn't know.

### What Is There to Lose by Giving People with Life-Threatening Diseases Like AIDS and Terminal Cancer Access to Whatever Drugs They Want?

If we didn't test drugs—if people could take whatever drug they wanted without any testing—there would be no way to tell whether any of the

thousands, millions, of candidate drugs out there worked. So no one would ultimately benefit.

For people with life-threatening illnesses, even the patient groups don't agree on where the right balance is between identifying treatments that will really improve patients' health and allowing people to have immediate access to experiment with drugs that might work for them.

I think AIDS is a good example. We had a lot of discussions with the AIDS activists early on about access

anything with no testing, we'd still be at the same point so much later into the epidemic: Everyone would have total availability to all drugs, but we wouldn't know what worked.

Some of the AIDS activists have actually told us they want more rigorous testing because, as they study their disease and the treatments, they realize they need information to make choices about which drugs they should take, even among the approved drugs. They want CDER to mandate a greater number of big

So, although some other kinds of speech are less restricted, things that are promotional in nature may have certain constraints legitimately put on them.

For example, drug labeling and advertising must be balanced about a drug's risks and benefits and not be misleading. In my opinion, consumers want truthful information, not hype.

Because people would like to receive all the latest information about a drug from the manufacturer, there has been a lot of debate about uses that are considered "off-label"—not approved by CDER. Obviously, medical science doesn't happen in spurts, but continuously. After a drug is put on the market, health professionals continuously experiment with new uses. We think that is appropriate and don't want to restrict that kind of use of drugs. But we don't want manufacturers to promote these uses to consumers until they are proven safe and effective.

The FDA Modernization Act allows manufacturers to provide physicians with articles from scientific journals and textbooks about new uses if they are conducting a study on the drug's new use or they promise to conduct one in the near future. To help the situation, we've put out a guidance document on how much information a manufacturer needs in order to get a new use on the label. We are also being very aggressive in getting new uses approved for people who were traditionally excluded from drug testing—children, women of child-bearing age, and the elderly. New uses have been approved in the latter half of the 1990s at more than double the rate they were approved in the first half. We think that manufacturers are motivated to submit applications for new uses because they know that we have been approving them promptly if they are found to work.

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to treatments. FDA put together many programs to allow people early access to those drugs even before they were approved.

But at the same time, companies pursued testing to see if these agents worked. Ultimately, some drugs were dropped because they didn't work or because they were so toxic that the risks outweighed the benefits. Ultimately, good drugs were found and then approved by CDER.

Now we're decreasing mortality with HIV. So every person with HIV has a path of drugs to take that he or she knows will work to improve health and has been proven to do so. If we'd gone down the other path, and everyone had been able to try

trials that would include combination therapy. "What if I start this combination early, versus if I take this single drug first? Which would help me to be in better health 10 years from now?" Those are the kinds of questions they want answered, and you can't answer those questions unless you do scientific testing.

### **Isn't CDER Infringing on Drug Marketers' Freedom of Speech When the Agency Restricts What Is Said in Drug Labeling and Advertising?**

There is a category of speech called "commercial speech," used when you're making a sales pitch.

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#### What Else Can FDA Do to Shorten Drug Development Times?

What we can do is evaluate our standards to make sure that all the information we require is absolutely necessary and that there are no unnecessary requirements. And we must be very clear about what information is required at each stage of drug development. The clearer we are, and the more universal the standards, the easier drug development will be.

Also, the United States, Japan, and the European Union have been negotiating to standardize technical requirements for human drugs under the International Conference on Harmonization (ICH). Companies then won't have to repeat tests unnecessarily.

What harmonization among countries means is that data that a drug company collected to submit to, say, Japanese authorities will be the same or similar data as that required for CDER. It means reducing the amount of testing, but each country would still make its own decision about whether to approve a drug. So far under the ICH, major progress has been made toward standardizing the information that is filed about

side effects so that unexpected side effects may be detected earlier, and standardizing the kinds of safety testing in humans that are required.

But to say CDER alone should decrease development times of drugs would be a big stretch. Because pharmaceutical companies develop the drugs, not CDER, much of the burden for shortening development times and decreasing development costs lies with them.

#### Is the Center's Rapid Approval of Drugs Compromising Public Safety?

Everybody has to be aware that the clinical testing—the premarket testing of drugs—will not detect all the problems. It just can't. It won't detect some of the problems with the drug or some of the toxicities with some drugs. This fact is something that the public and the medical and pharmacy community really needs to understand better.

Why doesn't testing detect them all? Well, it isn't because the review process breaks down. First of all, it's because some of the events are rare. They may occur in one out of 10,000 people. So, if you test 5,000 people in your clinical development program, you probably won't see it.

Even if you test 10,000, you may not see it; or if you see it, you wouldn't believe it was related. We know this is going to happen sometimes after a drug is approved.

Second, some problems with drugs are caused by the way they're used outside of the parameters for which they're approved. I think the diet drug fenfluramine is a good example. It caused heart-valve problems. It was only approved for three months' use, but people used it for longer periods of time.

Also, sometimes we encounter errors in the use of the drug, for example, medication errors that were hard to foresee prior to approval. Maybe the name, even though we look at the names, was too close to another drug name, and once they get out on the market, they get mixed up.

For all these reasons, a vigorous program is needed after drugs are marketed, to detect these safety problems and to correct them as soon as possible. We have a spontaneous reporting system through which people can report all these problems to the agency. We get a tremendous number of reports—about a quarter a million a year.

We are upgrading this system. Because it has a very large number of reports, it is hard to deal with them all. We're totally computerizing this, and with the industry, we're trying to move toward electronic submission of all of the reports. This will help us analyze them faster and disseminate information better.

#### What's in the Future for CDER?

First, we are moving toward a completely electronic submission and review environment by 2002. Right now, a typical drug application has so much paper that we need a forklift to transfer it. With electronic submissions, we'll be able to fit it all on a CD-ROM or two. This means less

## Traditional Expectations for the Drug Regulatory System:

All marketed drugs are effective and safe within the context of their use.

Human drugs are of high quality.

Generic competition keeps drug prices reasonable.

All advertising and promotion of drugs are informative and are not false or misleading.

## Evolving Expectations for the System:

Patients who lack alternatives have access to investigational drugs.

High-quality information about how to use drugs is available, including information on children, elderly patients, and other groups.

Robust drug development programs that thoroughly protect human subjects flourish and are productive.

paperwork for everyone and quicker, more accurate reviews.

Second, I think CDER is really going to have to step up to the plate in the new world of medical care, where managed care is the paradigm of how patients are being taken care of in this country. We need to think about how our information and how our role of drug approval and regulation fit in with the newly emerging healthcare system in the United States.

How does the pharmaceutical firm's role in the managed care industry fit with FDA's traditional method of regulating what pharmaceutical firms can say about their drugs? This, again, is a very controversial issue. The public has a lot of issues about having their medicines switched.

Antibiotic resistance is something you'll be hearing about in upcoming years. We're getting to the point where we have new, effective antibiotics that may be the only antibiotic that can treat a certain bug. Should this antibiotic be allowed to be administered widely throughout the country to the point where it, too, has resistance developed to it? What should be the national approach to this upcoming problem of antibiotic resistance?

More and more drug development is aimed at treating chronic diseases. We can't ask drug developers to study a drug for the entire lifetime of a patient with a chronic disease. They may study it for one or two years total per patient. So what should we do after that drug is approved? How much information should be collected, and what happens if you take the drug for 5 years, or 10 years, or 20 years? What should we do? And what power should we have to compel that kind of information to be collected?

Finally, in my opinion, effective communication is linked to drug

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safety. If we can get the information about potential or actual problems with drugs out to doctors, patients, and those people who need it, then drugs are going to be safer. If people are in the dark, then misuse of drugs will occur more frequently. We are working toward improving prescription drug labeling and improving over-the-counter drug labeling.

Most people cannot have missed the increased prominence of direct-to-consumer advertising recently. In addition, there's a private, ongoing, voluntary process to have consumer information available at the pharmacy for prescription drugs. So when consumers fill their prescriptions, they will receive information sheets. This process is being monitored by the FDA to ensure that it happens adequately. This is a very important issue for drug safety: that consumers get adequate information on how to use their drugs and that the information they get is correct.